

REMARKS/ARGUMENTS

The Final Office Action dated 07/19/2004 rejected claims 1-7 and 14-22. No claims were indicated as allowable. Claims 8-13, 23-26 and 31-34 were withdrawn pursuant to a species election in Paper No. 9, 07/01/2003. The species related to different bacterial species. Claims 1-7 and 14-22 were pending and under examination. For the convenience of the Examiner, the rejections set forth in the presently outstanding Office Action are set forth below in the order found in that paper.

Rejections Maintained

1. Rejection of Claims 1-7 and 14-19 under 35 USC 102(e) over Miller III, et al. 5,731,196 in light of Heithoff et al

The Examiner maintained that “Since there is a close overlapping relationship between PhoP and Dam regulatory genes, inherently alterations of the Salmonella genome affecting virulence in PhoP are anticipated in the present invention.” Miller III et al. are said to teach a bacterial cell, e.g. *S. typhi*, including a virulence attenuating mutation in a gene regulated by a PhoP regulatory system in a vaccine. Heithoff et al. are said to indicate that Dam activity of Salmonella “regulates the expression of at least 20 genes known to be induced during infection (inherently at the transcriptional level) wherein a subset of these genes are among those activated by the PhoP global virulence sites, as evidenced by alteration in DNA methylation patterns (Abstract) and more specifically taught at Fig. 2 at page 968. Therefore it appears without evidence to the contrary that PhoP mutations do inherently disclose the claimed invention.”

Response

PhoP mutations are not *dam* gene mutations, as presently claimed. Furthermore, as stated in Heithoff, p. 69, “However, this regulation does not occur at the transcriptional level, because Dam does not alter PhoP expression, nor does PhoP alter Dam expression.”

Thus bacteria having mutations in PhoP may have altered methylation patterns, but they do not have altered Dam expression. The present claims are not and can not be anticipated by Miller III, et al.

2. Rejection of Claims 1-7, 14-18 and 22 under 35 USC 102(e) as anticipated by Miller et al. 5,843,426 in light of Heithoff et al.

Miller et al. is said to teach a Salmonella vaccine with a mutation in a PhoP region. The Examiner did not accept Applicants' showing that mutations in the PhoP gene do not affect Dam expression, for the reasons provided in the previous rejection.

Response

The Miller '426 Abstract states that "The invention features a Salmonella cell the virulence of which is attenuated by a deletion of a portion of the PhoQ gene and Salmonella cells having a deletion of the PhoQ gene and a deletion of the PhoP gene. The invention also features vaccines comprising such bacteria. "

The *Dam* gene is nowhere mentioned in this reference. As stated above, it is known in the scientific literature that, although both PhoP and Dam cause methylation, the genes do not regulate each other. Mutations in PhoP have no effect on the expression of the *dam* gene.

Thus this reference does not anticipate the presently claimed invention.

3. Rejection of Claims 1-7 and 14-22 under 102(b) over Miller and Mekalanos, J. Bacterio. In light of Heithoff.

Miller and Mekalanos are said to teach a composition comprising a pharmaceutically acceptable excipient and attenuated *S. typhimurium* as an immunogenic composition, allowing mice to survive an oral challenge. They further teach that mutations in PhoP attenuate virulence. This was said to be inherent anticipation in that these bacteria inherently possess the same structural and functional characteristics.

Response

As stated, mutations in *PhoP* do not cause the same functional or structural alterations as mutations in *dam*. *PhoP* mutations may cause alterations in methylation patterns, but they are not the same alterations in methylation patterns as are caused by alteration of the *dam* gene. As stated in Heithoff, p. 69, alterations in PhoP do not alter *dam* gene expression.

4. Provisional Double Patenting Rejection

Claims 1-7 and 14-22 were rejected for obviousness-type double patenting over claims 1-46 of copending application 09/928,227 and over claims 1-29 of copending application 09/927,788. This was a provisional rejection, because the conflicting claims have not in fact been patented.

Response

A terminal disclaimer is produced herewith.

Conclusion

It is believed that the present Amendments place the application in condition for allowance. Since the Office Action of 7/19/2004 was final, an RCE is submitted herewith to ensure entry of the present Amendment.

New claim 35 is supported in the specification and in previously presented claims. Allowance of claims 14-20, 22 and 35 is respectfully requested. Rejoinder of species in claims 8-13, 23-26 and 31-34 upon allowance of a genus claims is also requested. Such action, as well as the timely issuance of a Notice of Allowance is earnestly solicited. If a telephone conference would be useful in this case, the Examiner is invited to call the

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undersigned at the number below.

Respectfully submitted,

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